



Study Protocol



A Real-world Study Protocol for Treating COVID-19 Convalescent Patients with Traditional Chinese Medicine Based on Syndrome Differentiation

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Abstract

Background and objectives: COVID-19 has resulted in significant long-term sequelae in convalescent patients, impacting overall quality of life. Traditional Chinese medicine (TCM) has shown promise in managing post-COVID-19 symptoms through syndrome differentiation. This study aimed to evaluate the efficacy and safety of TCM in COVID-19 convalescent patients in a real-world setting.

Methods: This prospective, real-world study will be conducted at Guangdong Provincial Hospital of Traditional Chinese Medicine. A total of 528 COVID-19 convalescent patients will be recruited and divided into two groups: a control group receiving routine Western medical treatment and an intervention group receiving additional TCM treatment based on syndrome differentiation. Patients will be assessed for three major TCM syndromes: *Lung-Spleen Qi* Deficiency, *Qi-Yin* Deficiency, and *Cold Phlegm Obstructing the Lung*, with corresponding TCM prescriptions administered accordingly. The primary outcome measure will be the improvement in clinical symptom scores based on a TCM symptom scoring system. Secondary outcomes will include changes in laboratory tests, imaging studies, heart function classification, and quality of life scores. Safety will be assessed through liver and kidney function tests and adverse event monitoring.

Results: The study is expected to demonstrate that TCM treatment, based on syndrome differentiation, can significantly improve clinical symptoms and overall health in COVID-19 convalescent patients compared to routine Western medical treatment. These findings will provide evidence for integrating TCM into post-acute COVID-19 care.

Conclusions: This study will contribute to the evidence supporting TCM as an effective treatment for post-COVID-19 syndrome, enhancing patient outcomes and informing comprehensive recovery strategies.

Keywords: Traditional Chinese medicine; COVID-19; Convalescent patients; Syndrome differentiation and treatment; Real-world study; RWS.

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Introduction

COVID-19 is an acute respiratory infectious disease caused by the novel coronavirus (SARS-CoV-2). Globally, the number of confirmed cases has exceeded 600 million, with over seven million deaths reported. In China, the number of confirmed cases has surpassed two million. As the number of recovered COVID-19 patients increases, the emergence of post-acute sequelae has become a new global health challenge.^{1,2} These sequelae affect multiple systems, including the respiratory, circulatory, nervous, digestive, and psychological-cognitive systems, and manifest as a range of symptoms such as fatigue, cough, shortness of breath, poor appetite, insomnia, low-grade fever, night sweats, constipation or diar-

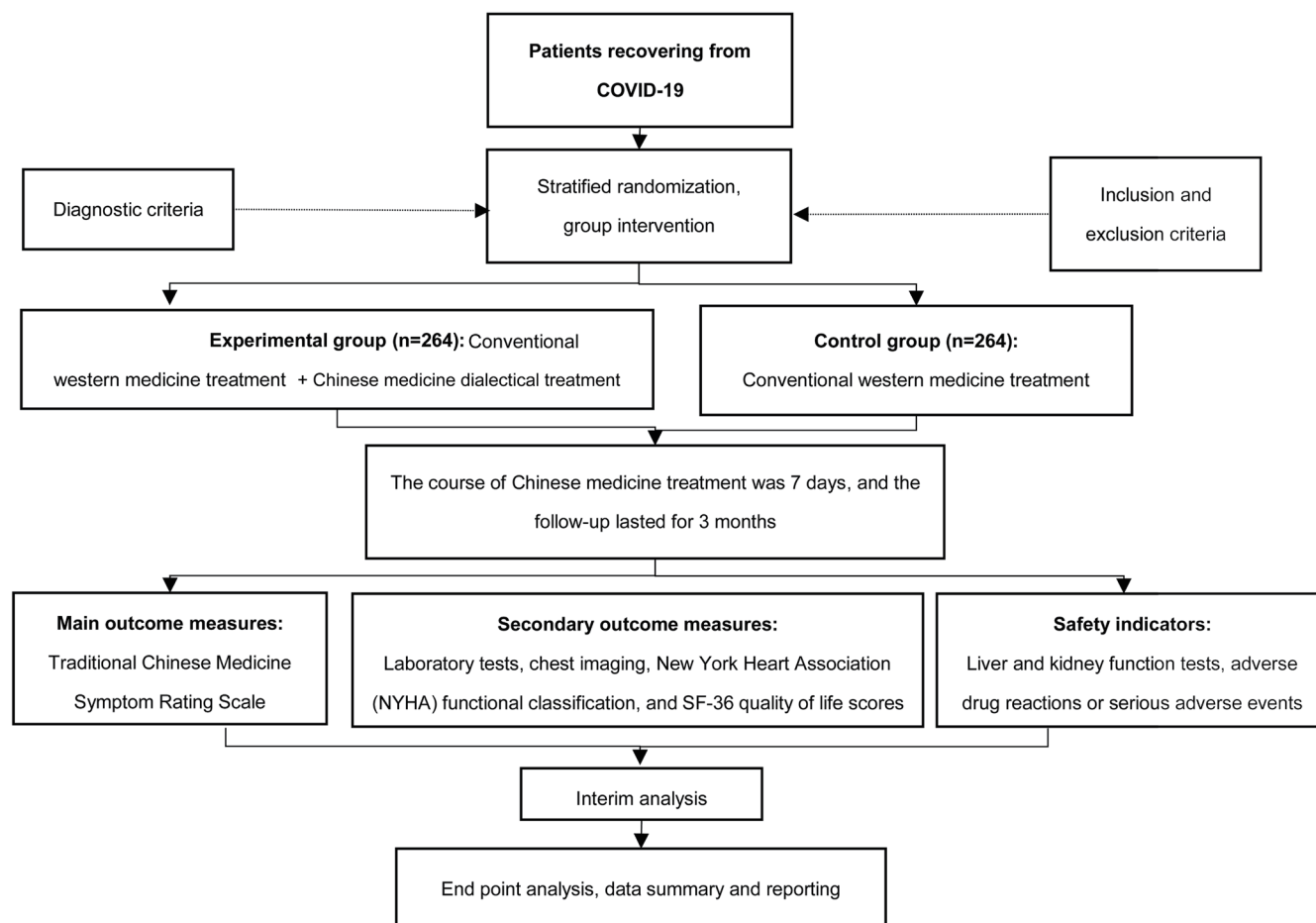


Fig. 1. Technology roadmap.

rhea, chest tightness, palpitations, chronic bleeding, and sensory or motor impairments.^{3,4} The duration and severity of these symptoms vary, significantly impacting both physical and mental health and posing challenges to societal development.

In traditional Chinese medicine (TCM), novel coronavirus pneumonia (COVID-19) falls under the category of a “damp toxin epidemic,” with dampness as the primary etiological factor. The main pathogenesis involves obstruction of the lungs by damp toxins. During the clinical recovery phase, common syndromes include *Lung-Spleen Qi* Deficiency Syndrome, *Qi-Yin* Deficiency Syndrome, and *Cold Phlegm* Obstructing the Lung Syndrome. As symptoms vary among individuals, syndrome differentiation-based treatment may lead to better therapeutic outcomes.

Despite increasing recognition of post-COVID-19 sequelae, there remains a significant research gap regarding the role of TCM in managing these long-term complications. Specifically, there is a lack of robust real-world evidence on the effectiveness of TCM in addressing post-acute sequelae of COVID-19. While TCM has been widely used in the treatment of acute COVID-19 cases in China, with positive outcomes,^{5,6} its role in post-recovery care, particularly in real-world clinical settings, remains underexplored.

This study aimed to observe and comprehensively evaluate the therapeutic effects of TCM syndrome differentiation and treatment in COVID-19 convalescent patients in a real-world clinical setting.

The findings will provide objective clinical evidence on the efficacy of TCM in treating post-COVID-19 conditions.

Materials and methods

Study design

This real-world study will be conducted at Guangdong Provincial Hospital of Traditional Chinese Medicine. A total of 528 COVID-19 convalescent patients will be recruited from either outpatient clinics or inpatient departments. The study follows a prospective design, incorporating both an intervention group and a control group. (Fig. 1).

Participants

Inclusion criteria

- Patients who meet both Western and TCM diagnostic criteria;
- Age between 18 and 80 years;
- Normal communication ability and willingness to participate in the study and follow-up;
- Written informed consent obtained.

Exclusion criteria

- Patients currently using other TCM formulations or participat-

- ing in other clinical trials;
- Pregnant or breastfeeding women;
- Patients with known allergies to the study medications or a history of allergic constitution;
- Patients with severe primary diseases of the liver, kidneys, or hematopoietic system.
- Patients with uncontrolled bronchial asthma, chronic obstructive pulmonary disease, sleep apnea, respiratory failure, or other chronic hypoxic conditions.

Diagnostic criteria

Western medical diagnosis

Based on the COVID-19 Diagnosis and Treatment Protocol (Trial Version 10), patients are considered to be in the convalescent phase when their condition has significantly improved, with stable vital signs, a normal body temperature for over 24 h, and significant improvement in pulmonary imaging showing resolution of acute exudative lesions. Additionally, they should be able to transition to oral medication without any complications requiring further intervention.

TCM syndrome differentiation diagnosis

Based on the “TCM Syndrome Diagnosis Standard for COVID-19 (Trial Version)” and clinical recovery phase criteria:

- *Lung-Spleen Qi* Deficiency Syndrome: Characterized by cough with scanty sputum, shortness of breath or fatigue exacerbated by activity, low-grade fever or spontaneous sweating, poor appetite, abdominal bloating, loose stools, a pale and swollen tongue with a white greasy coating, and a deep and thin pulse.
- *Qi-Yin* Deficiency Syndrome: Characterized by dry cough with scanty sputum, shortness of breath or fatigue exacerbated by activity, dry mouth or throat, spontaneous or night sweats, low-grade fever or heat in the palms and soles, a thin and rapid pulse, and a red or pale tongue with scanty or patchy coating.
- *Cold Phlegm* Obstructing the *Lung* Syndrome: Characterized by chills (with or without fever), headache, body aches, cough with white sputum, poor appetite, abdominal bloating, sticky or loose stools, a white greasy or slippery tongue coating, and a floating and tight or soft pulse.

Implementation process of syndrome differentiation

The Standard for TCM Syndrome Diagnosis and Treatment of Pneumonia Infected by Novel Coronavirus (Trial), in conjunction with expert clinical consensus, was utilized to implement a double-blind syndrome differentiation process:

1. Initial diagnosis differentiation:
 - Performed independently by two attending physicians or higher-level TCM specialists.
 - Four diagnostic parameters (tongue, pulse, symptoms) were collected and input into the structured electronic medical record system.
 - Syndrome differentiation criteria: The framework included an eight-line syndrome differentiation, zang-fu dialectical framework, and etiological dialectical framework. This resulted in three primary syndromes: deficiency of lung and spleen, deficiency of Qi and Yin, and cold phlegm obstructing the lungs.
2. Check and verification:
 - Divergent cases were submitted to an expert panel (≥ 2 deputy directors or higher-level TCM physicians) for consultation.

Interventions

Control group

Routine symptomatic treatment includes cough suppression and expectoration. Risk factors will be managed, including smoking cessation, blood pressure, blood glucose, and lipid control. Health education and lifestyle adjustments will also be provided, emphasizing adequate sleep with a regular circadian rhythm, low-salt and low-fat diets, sufficient energy and nutritional intake, and structured exercise.

Symptomatic pharmacological treatment

1. *Antitussives*: *Dextromethorphan hydrobromide* (15–30 mg orally every 6–8 h, maximum 120 mg/day) for non-productive cough. *Codeine phosphate* (15–30 mg orally every 4–6 h, maximum 120 mg/day) for refractory cough, limited to short-term use (less than seven days) due to dependency risk.
2. *Mucolytics*: *Ambroxol hydrochloride* (30 mg orally three times daily) or acetylcysteine (600 mg orally once daily) for productive cough.

Comorbidity and risk factor management

1. *Hypertension*: Target blood pressure $<140/90$ mmHg using angiotensin-converting enzyme inhibitor / angiotensin ii receptor blocker (e.g., losartan 50 mg/day) as first-line therapy.
2. *Diabetes Mellitus*: Target fasting glucose 4.4–7.0 mmol/L with metformin (500–850 mg twice daily).
3. *Hyperlipidemia*: Atorvastatin (20 mg/day) for low-density lipoprotein cholesterol ≥ 2.6 mmol/L.

Standardized lifestyle intervention

1. *Exercise*: aerobic training (such as brisk walking or tai chi) for 30 m/day, at least five days per week.
2. *Nutrition*: Protein intake ≥ 1.2 g/kg/day (e.g., lean meat, legumes). Sodium restriction (<2.3 g/day) and potassium-rich foods (e.g., bananas, spinach).
3. *Sleep management*: It is recommended to ensure 7–9 h of continuous or segmented sleep (including naps) daily, allowing ± 1 -h individual variations.

Intervention group

In addition to routine treatment provided to the control group, the intervention group will receive TCM syndrome differentiation and treatment based on the following herbal formulas:

- *Lung-Spleen Qi* Deficiency Syndrome: Prepared with Pinellia ternata (Ban Xia) 9g, Citrus reticulata (Chen Pi) 10g, Codonopsis pilosula (Dang Shen) 15g, Astragalus membranaceus (Huang Qi) 30g, Atractylodes macrocephala (Bai Zhu) 10g, Poria cocos (Fu Ling) 15g, Amomum villosum (Sha Ren) 6g (added later), and Glycyrrhiza uralensis (Gan Cao) 6g.
- *Qi-Yin* Deficiency Syndrome: Prepared with Adenophora stricta (Nan Sha Shen) 10g, Glehnia littoralis (Bei Sha Shen) 10g, Ophiopogon japonicus (Mai Dong) 15g, Panax quinquefolius (Xi Yang Shen) 6g, Schisandra chinensis (Wu Wei Zi) 6g, Gypsum fibrosum (Sheng Shi Gao) 15g, Phragmites communis (Dan Zhu Ye) 10g, Mulberry leaf (Sang Ye) 10g, Phragmites communis (Lu Gen) 15g, Salvia miltiorrhiza (Dan Shen) 15g, and Glycyrrhiza uralensis (Gan Cao) 6g.
- *Cold Phlegm* Obstructing the *Lung* Syndrome: Prepared with Belamcanda chinensis (She Gan) 9g, Ephedra sinica (Ma Huang) 6g, Zingiber officinale (Gan Jiang) 15g, Aster tataricus (Zi Wan) 30g, Inula helenium (Kuan Dong Hua) 30g, Schisandra chinensis (Wu Wei Zi) 15g, Pinellia ternata (Ban Xia) 9g,

Peucedanum praeruptorum (Qian Hu) 15g, Stemona tuberosa (Bai Bu) 15g, Perilla frutescens (Su Zi) 9g, Alpinia katsumadai (Cao Dou Kou) 15g, and Fritillaria unibracteata (Chuan Bei Fen) 3g (dissolved). The TCM formulas will be prepared using the traditional decoction method. The herbs will be added to 800 mL of cold water and brought to a boil over high heat (武火). Once boiling, the heat will be reduced to a gentle simmer (文火), and the mixture will be simmered for 30–45 m until the liquid is reduced to approximately 400–500 mL. The decoction will then be strained and divided into two equal doses, to be administered twice daily. A fresh decoction will be prepared each day to ensure optimal therapeutic effect. This process will be repeated for seven consecutive days, and the decoction should be consumed while still warm to facilitate absorption and effectiveness.

Treatment adherence monitoring

This study employs a standardized patient log for compliance management, implemented as follows:

1. **Log design:** The “Traditional Chinese Medicine Treatment Compliance Record Manual” has been designed, which includes the date and daily execution details.
 - Daily TCM medication adherence;
 - Western medicine symptomatic medication adherence;
 - Management of comorbidities and risk factors;
 - Non-pharmacological therapy adherence;
 - Symptom changes and adverse reaction recording section;
 - Treatment feedback section.
2. **Data quantification:** Compliance rate calculation formula: (Actual number of completed treatment items/Required number of treatment items) $\times$ 100%

Definitions:

 - Full compliance: $\geq 95\%$ with no critical treatment omissions;
 - Partial compliance: 80–94%;
 - Non-compliance: $< 80\%$.

Outcome measures

Patients will be followed up for three months. The following outcomes will be assessed before and after treatment:

- **Primary Outcome Measures: Improvement in clinical symptom scores using a TCM symptom score scale (cough, fever, palpitations, dizziness, chest tightness, shortness of breath, fatigue) (Table 1).**

Efficacy evaluation criteria (Table 2):

 - In this study, the percentage of total symptom decline before and after treatment was used to determine the efficacy, and the threshold was defined as follows^{7–9}:
 - Significant effect: Total score decreased by $\geq 50\%$ (reflecting substantial improvement in symptoms);
 - Effective: Total score decreased by 20% to 49% (minimal clinically significant difference, MCID);
 - Invalid: Total score decreased by $< 20\%$.
 - Secondary Outcome Measures: Changes in laboratory tests (complete blood count, urinalysis, blood gas analysis, biochemical markers, C-reactive protein, cardiac enzymes, troponin, proBNP, D-dimer), chest imaging findings (X-ray or computed tomography), New York Heart Association (NYHA) heart function classification (Table 3), and SF-36 quality of life score. Safety indicators will include liver and kidney function tests, with documentation of any adverse drug reactions or serious adverse events.

Data collection and management

Data will be collected using standardized case report forms and

entered into a secure database. All data will be anonymized to protect patient confidentiality. Regular monitoring and quality control measures will ensure data accuracy and integrity.

Sample size and statistical analysis

Sample size calculation

The sample size was determined using an analysis of covariance framework to adjust for baseline covariates in this real-world study. Based on a conservative effect size of Cohen's $f = 0.25$ (small-to-moderate effect) derived from prior TCM symptom improvement studies,¹⁰ a significance level ($\alpha = 0.05$, two-tailed), 90% power ($\beta = 0.10$), and an anticipated 30% variance explained by covariates ($R^2 = 0.30$), the initial calculation yielded 468 participants. Adjustments included a design effect of 1.2 for multicenter clustering and a 15% attrition rate,¹¹ resulting in a required sample of 662 participants. The final target sample size was set at 528 participants (264 per group), based on feasibility and sensitivity analyses (using PASS 15.0), ensuring $\geq 85\%$ power for effect sizes ≥ 0.28 . Pilot data ($n = 50$) indicated a higher covariate explanatory power ($R^2 = 0.35$), supporting these adjustments.

Statistical methods

All analyses were performed using R 4.3.0 (packages: lme4 for mixed models, mice for multiple imputations) and SPSS 29.0. Continuous variables were summarized as mean $\pm$ standard deviation and compared between groups using analysis of covariance, adjusting for baseline covariates (age, sex, baseline symptom score, and comorbidities). Non-normally distributed data were analyzed via Mann-Whitney U tests. Categorical variables were assessed using chi-square tests or Fisher's exact test (for expected cell counts < 5).

The primary analysis evaluated differences in symptom scores between treatment and control groups, adjusted for covariates. Secondary analyses examined changes in laboratory parameters, imaging findings, heart function classification, and quality of life scores. Missing data were addressed through both the last observation carried forward method and multiple imputation (MICE algorithm with five imputed datasets). Sensitivity analyses confirmed robustness across imputation methods.

Reporting standards

The analysis adhered to the CONSORT extension for cluster trials and the RECORD Statement for real-world evidence.^{12,13} An interim analysis at 50% enrollment ($n = 264$) was planned to reassess assumptions and adjust parameters if necessary.

Ethics and consent

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). The study protocol has been reviewed and approved by the institutional ethics committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (No. ZF2023-037). Written informed consent was obtained from all participants. This study is registered at <http://itmctr.ccebtcm.org.cn/>. The registration identification number is ITMCTR2025001974.

Discussion

This study addresses a critical gap in the management of COVID-19 convalescent patients by exploring the application of TCM in post-acute care. While global attention has predominantly focused on the acute phase of COVID-19, emerging evidence high-

Table 1. Score of traditional Chinese medicine symptom integral scale

Symptom item	Scoring criteria (numerical values = points)
Cough Symptom Scoring	
Daytime cough frequency	☐ 0=No cough ☐ 1=Occasional (≤ 3 episodes/day) ☐ 2=Intermittent (4–6 episodes/day) ☐ 3=Frequent (7–9 episodes/day) ☐ 4=Persistent (≥ 10 episodes/day)
Nighttime cough frequency	☐ 0=No cough ☐ 1=Occasional (≤ 1 episode/night) ☐ 2=Intermittent (2–3 episodes/night) ☐ 3=Frequent (4–5 episodes/night) ☐ 4=Persistent (≥ 6 episodes/night)
Duration of cough episodes	☐ 0=None ☐ 1= ≤ 1 minute/episode ☐ 2=1–3 minutes/episode ☐ 3=3–5 minutes/episode ☐ 4=Continuous (> 5 minutes)
Cough intensity	☐ 0=None ☐ 1=Mild (throat clearing only) ☐ 2=Moderate (controllable) ☐ 3=Severe (with flushing/tearing) ☐ 4=Violent (with vomiting)
Impact on daily activities	☐ 0=No impact ☐ 1=Mild interference (activities continued) ☐ 2=Activities paused ☐ 3=Rest required ☐ 4=Complete activity cessation
2. Fever (highest body temperature)	☐ 0=Afebrile ($\leq 37.3^{\circ}\text{C}$) ☐ 1=Low-grade ($37.4\text{--}38.4^{\circ}\text{C}$) ☐ 2=Moderate ($38.5\text{--}39.0^{\circ}\text{C}$) ☐ 3=High ($\geq 39.1^{\circ}\text{C}$)
3. Chest pain/tightness	☐ 0=None ☐ 1=Mild (post-exertion) ☐ 2=Moderate (occurs at rest) ☐ 3=Severe (persistent respiratory impairment)
4. Dyspnea	☐ 0=None ☐ 1=During brisk walking ☐ 2=During daily activities (e.g., stair climbing) ☐ 3=At rest
5. Sputum production	☐ 0=None ☐ 1=Minimal (≤ 5 mL/day) ☐ 2=Moderate (5–10 mL/day) ☐ 3=Copious (> 10 mL/day)
6. Functional status	☐ 0=Normal ☐ 1=Mild fatigue (manages routine activities) ☐ 2=Reduced activity tolerance ☐ 3=Bedridden $> 50\%$ daytime

Total score calculation and efficacy evaluation. 1. Scoring Ranges: 0–35 points; 2. Therapeutic Efficacy Criteria. Efficacy is determined by the percentage reduction in the total score between baseline and post-treatment assessments: (1) Markedly effective: $\geq 50\%$ reduction; (2) Effective: 20–49% reduction; (3) Ineffective: $< 20\%$ reduction.

lights the substantial burden of long-term sequelae affecting convalescent patients. The significance of this investigation lies in its alignment with TCM's historical strength in managing complex chronic conditions through syndrome differentiation and individualized treatment strategies.¹⁴ By adopting a personalized therapeutic approach targeting three major TCM syndromes (*Lung-Spleen*

Qi Deficiency, *Qi-Yin* Deficiency, and *Cold Phlegm* Obstructing the Lung), this protocol offers a structured framework for addressing the heterogeneous manifestations observed in post-COVID recovery.

The therapeutic rationale for employing TCM in convalescent care stems from its documented efficacy during the acute phase

Table 2. Treatment compliance evaluation

Date	Treatment compliance evaluation									
	Whether to use traditional Chinese medicine intervention?									
	Use of traditional Chinese medicine	Symptomatic treatment of Western medicine	Management of complications	Risk factor management		Lifestyle intervention		Dietary regulation (protein, sodium)		Aerobic exercise (30 minutes)
Day 1, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 2, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 3, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 4, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 5, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 6, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes
Day 7, _ _ _	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes	☐ _0 ☐ _No, ☐ _1Yes

Changes in symptoms and abnormal reactions recording column. Treatment experience feedback column.

Table 3. New York Heart Association for the heart functional classification

Classification category
<i>I. Class I:</i> Patients have heart disease, but their daily activities are not limited. General physical activities do not cause excessive fatigue, palpitations, dyspnea, or angina.
<i>II. Class II:</i> Patients with heart disease have mild limitations in physical activity. They have no symptoms at rest, but general physical activities cause excessive fatigue, palpitations, dyspnea, or angina.
<i>III. Class III:</i> Patients have heart disease, resulting in significant limitations in physical activity. They have no symptoms at rest, but activities less than general physical activities cause excessive fatigue, palpitations, dyspnea, or angina.
<i>IV. Class IV:</i> Patients with heart disease are unable to perform any physical activities and experience heart failure symptoms even at rest, which worsen with physical activity.

of COVID-19 in China and its theoretical foundation in restoring physiological balance. The lingering symptoms characteristic of post-acute COVID-19 syndrome align with TCM's conceptualization of residual pathogenic factors and compromised Qi. This congruence between clinical manifestations and TCM pathomechanisms provides a logical basis for intervention, particularly through herbal formulations that target specific syndrome patterns.^{15,16} The selection of syndrome-specific treatments reflects an adaptive strategy to address the multidimensional nature of post-viral recovery.

A notable methodological innovation of this study is its real-world design, which enhances ecological validity by mirroring actual clinical practice. Unlike conventional randomized controlled trials with restrictive eligibility criteria, this approach accommodates the inherent diversity of patient presentations in post-COVID care settings. The comprehensive assessment protocol, which incorporates both subjective symptom evaluations (TCM symptom scores, Pittsburgh Sleep Quality Index, and Modified Medical Research Council Dyspnea Scale) and objective biomarkers (lymphocyte counts, High-sensitivity C-Reactive Protein, and computed tomography scans), strengthens the robustness of outcome measurement. This dual evaluation system helps counterbalance potential limitations associated with subjective reporting while maintaining clinical relevance.

However, several methodological considerations warrant attention. The pragmatic study design inherently introduces variability in treatment adherence and patient characteristics, which may complicate outcome interpretation. The multivariate nature of TCM interventions, particularly the concurrent use of multiple syndrome-specific formulas, presents analytical challenges in isolating individual treatment effects. These limitations are partially mitigated through standardized data collection procedures and systematic safety monitoring. Additionally, while subjective symptom scales remain essential for assessing patient-reported outcomes, their reliability concerns are counterbalanced by incorporating laboratory and imaging biomarkers.¹⁷⁻¹⁹ The single-center design represents another limitation, suggesting the need for future multi-center validation to enhance generalizability.

The implications of this research extend beyond immediate clinical applications. A successful demonstration of TCM's effectiveness in post-COVID care could stimulate mechanistic studies

elucidating the biological pathways underlying its therapeutic effects. This knowledge may facilitate the development of standardized TCM protocols amenable to integration with Western medical practices. Furthermore, the study's methodological framework provides a template for investigating TCM applications in other post-viral syndromes, potentially informing global rehabilitation strategies. Collaborative efforts between TCM practitioners and biomedical researchers will be crucial for advancing the evidence-based integration of traditional and modern therapeutic paradigms.^{5,20}

Future directions

Based on the findings of this real-world study, several promising directions will be considered in the further studies. First, mechanistic studies are warranted to elucidate the biological pathways underlying the mechanisms for herbal medicine. Second, extending follow-up periods beyond three months will be considered which will provide critical insights into the long-term benefits and sustainability of syndrome differentiation-based TCM interventions. Third, the development of standardized TCM protocols tailored to specific post-COVID syndromes may enhance reproducibility of the work. Finally, more studies are needed to evaluate the long-term effect for the integrative medicine. These efforts will not only advance evidence-based TCM but also inform global strategies for managing post-viral syndromes.

Conclusions

This study represents a step forward in integrating TCM into the management of COVID-19 convalescent patients. By providing evidence on the efficacy and safety of TCM syndrome differentiation and treatment, this research aimed to enhance the clinical management of post-COVID-19 symptoms and improve patient outcomes.

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Conflict of interest

The authors declare that there is no conflict of interest in the authorship and publication of this contribution.

Author contributions

Designed the study, finalized the manuscript (RYY, QL), collected information, constructed the dataset, completed the first version of the manuscript (QPD, XZ, ZLY, QL), and finished the manuscript

corrections (QL, RYY, XTX). All authors read, revised, and approved the final manuscript.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). The study protocol has been reviewed and approved by the institutional ethics committee of Guangdong Provincial Hospital of Traditional Chinese Medicine (No. ZF2023-037). Written informed consent was obtained from all participants. This study is registered at <http://itmctr.ccebtcm.org.cn/>. The registration identification number is ITMCTR2025001974.

Data sharing statement

All the data underlying the findings of our manuscript can be accessed by contacting the corresponding author with reasonable requests.

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